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# 1,3-Difunctionalizations of [1.1.1]Propellane via 1,2-Metallate Rearrangements of Boronate Complexes

Songjie Yu,<sup>†</sup> Changcheng Jing,<sup>†</sup> Adam Noble, and Varinder K. Aggarwal<sup>\*[a]</sup>

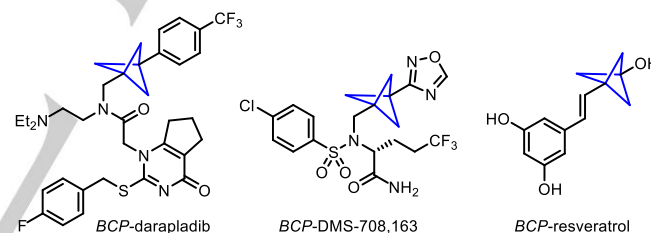
**Abstract:** 1,3-Disubstituted bicyclo[1.1.1]pentanes (BCPs) are valuable bioisosteres of *para*-substituted aromatic rings. The most direct route to these structures is via multi-component ring-opening reactions of [1.1.1]propellane. However, challenges associated with these transformations mean that difunctionalized BCPs are more commonly prepared via multistep reaction sequences with BCP-halide intermediates. Herein, we report three- and four-component 1,3-difunctionalizations of [1.1.1]propellane with organometallic reagents, organoboronic esters and a variety of electrophiles. This is achieved by trapping intermediate BCP-metal species with boronic esters to form boronate complexes, which are versatile intermediates whose electrophile-induced 1,2-metallate rearrangement chemistry enables a broad range of C–C bond-forming reactions.

Bicyclo[1.1.1]pentane (BCP) is a highly valuable motif in drug discovery.<sup>[1]</sup> Its size and conformational rigidity make 1,3-disubstituted BCPs bioisosteres of *para*-substituted benzene rings.<sup>[2]</sup> Structure activity relationships have shown that incorporating these sp<sup>3</sup>-rich surrogates of aromatic rings into drug candidates often results in more favorable pharmacokinetic properties, including improved aqueous solubility, increased membrane permeability, and higher metabolic stability (Scheme 1a).<sup>[3]</sup> Despite these desirable characteristics, application of 1,3-disubstituted BCP derivatives in drug discovery has been hindered by the limited number of concise synthetic routes to these motifs, in particular carbon-substituted analogues. One of the most powerful approaches to BCPs is via addition reactions to [1.1.1]propellane (**1**),<sup>[4]</sup> where the central  $\sigma$ -bond can be cleaved under both radical<sup>[5]</sup> and anionic pathways (Scheme 1b).<sup>[6]</sup> However, these reactions typically give monofunctionalized BCPs, or involve atom-transfer processes where, in addition to a carbon substituent, a halide group is introduced. Therefore, access to 1,3-disubstituted BCPs with two carbon substituents requires additional manipulations of the halide.<sup>[5c–e,7]</sup>

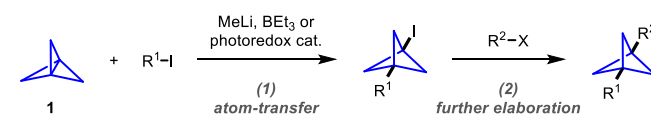
Direct transformation of **1** into unsymmetrical 1,3-disubstituted BCP derivatives via three-component coupling reactions is challenging because of competing oligomerization of the intermediate BCP radicals or carbanions.<sup>[4d,8]</sup> This is especially apparent for radical processes, of which there is only a single report by Uchiyama and co-workers describing a three-component aminoalkylation of **1**.<sup>[9]</sup> In contrast, BCP-Grignard

intermediates **2** are relatively stable to oligomerization with **1** and can be intercepted in palladium- or nickel-catalyzed cross-couplings,<sup>[10]</sup> copper-catalyzed alkylations,<sup>[11]</sup> or acylation reactions (Scheme 1c).<sup>[10b,10d,11]</sup> We were intrigued by the possibility of intercepting BCP-Grignards **2** with boronic esters to form BCP-boronate complexes **3** (Scheme 1d). These versatile intermediates can be utilized in a wide range C–C bond forming reactions via 1,2-metallate rearrangements,<sup>[12]</sup> therefore providing a significant expansion to the range of unsymmetrical 1,3-disubstituted BCP derivatives accessible in one step from **1**. Herein, we describe the successful realization of this approach in a transition metal-free three-component coupling between organometallic reagents, [1.1.1]propellane, and organoboronic esters. Furthermore, this strategy could be extended to a four-component coupling by trapping alkenyl BCP-boronate complexes with a range of electrophiles, enabling rapid access to highly functionalized BCP-derivatives.

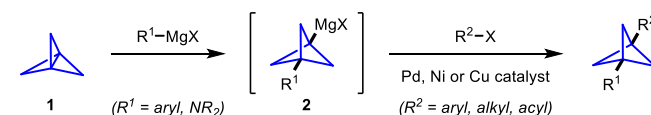
## a) Pharmaceutical derivatives containing 1,3-disubstituted BCPs



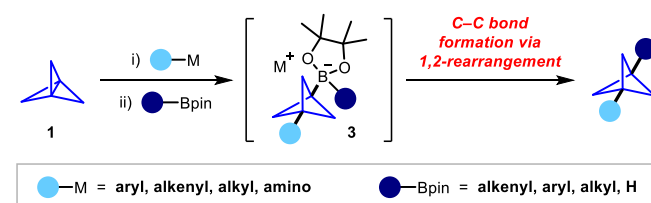
## b) Stepwise 1,3-difunctionalizations of [1.1.1]propellane



## c) Synthesis and reactions of BCP-Grignards generated from [1.1.1]propellane



## d) 1,2-Metallate rearrangements of BCP-boronate complexes (this work)



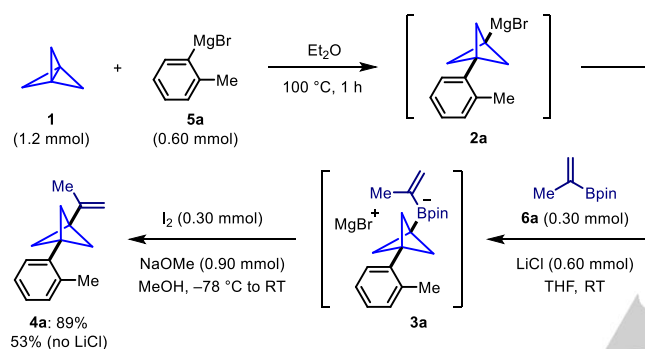
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**Scheme 1.** Synthesis of 1,3-difunctionalized bicyclo[1.1.1]pentanes.

Our initial studies focused on the reaction of BCP-Grignard reagent **2** in Zweifel olefinations with alkenylboronic esters to provide synthetically useful alkenyl-BCPs **4** (Scheme 2).<sup>[13]</sup> Using conditions developed by Knochel and co-workers,<sup>[10d]</sup> BCP-Grignard **2a** was conveniently accessed from 2-tolylmagnesium bromide (**5a**) and **1**. Addition of 2-propenylboronic ester **6a** formed boronate complex **3a**, which was subsequently reacted with iodine and sodium methoxide to promote 1,2-migration and boron elimination, yielding alkenyl-BCP **4a** in 53% yield. A recent report by Morken and co-workers found that boronate complex formation between vinyl Grignard reagents and pinacol boronic esters was greatly facilitated by LiCl,<sup>[14]</sup> which is known to increase the reactivity of Grignard reagents.<sup>[15]</sup> Pleasingly, addition of LiCl to BCP-Grignard **2a** prior to **6a** resulted in a much improved yield of **4a** of 89%.



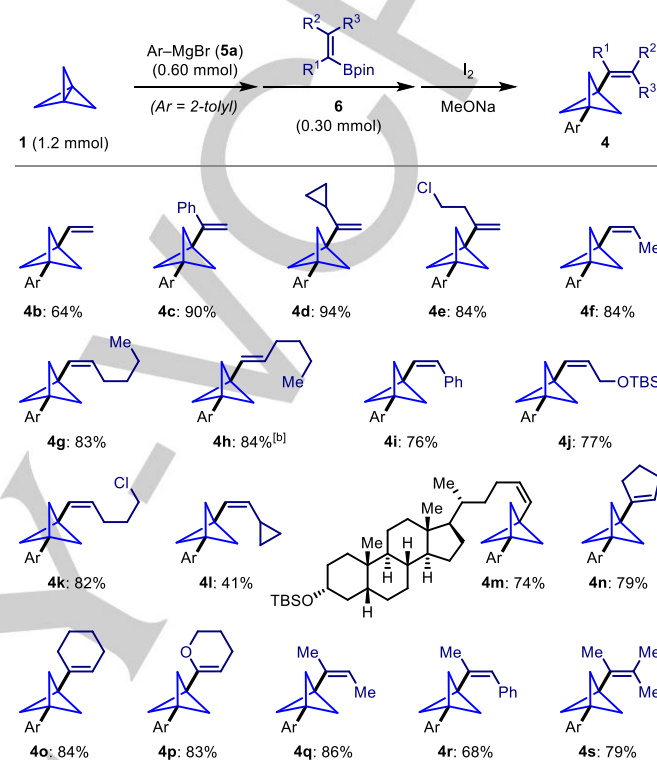
**Scheme 2.** Initial results for the BCP formation via Zweifel olefination.

With high yielding conditions in hand, we subsequently explored the scope of this three-component coupling (Table 1). Analysis of a range of alkenylboronic esters demonstrated the generality of the protocol, which could be used to access vinyl-BCP **4b** and a range of 1,1-disubstituted alkenes (**4c–e**) in good to excellent yields. For *E*-configured  $\beta$ -substituted alkenylboronic esters, Zweifel olefination leads to the corresponding *Z*-alkene products.<sup>[13c]</sup> This allowed the synthesis of a wide range of *Z*-alkenyl BCP derivatives (**4f–g**, **4i–m**), all with >95:5 *Z:E* selectivity. Conversely, using a *Z*-alkenylboronic ester provided *E*-alkenyl BCP product **4h**, again with excellent yield and stereocontrol (>95:5 *E:Z*). The functional group tolerance of the reaction was demonstrated by preparing alkenyl-BCPs containing silyl ethers (**4j**), halides (**4k**), cyclopropanes (**4l**), and complex natural product scaffolds, such as lithocholic acid derivative **4m**. Trisubstituted alkenes were also formed in high yields, including both cyclic (**4n–p**) and acyclic (**4q–r**) examples, with the latter being formed with excellent stereoselectivity (>95:5 *Z:E*). Finally, the Zweifel olefination could also be applied to the high yielding synthesis of tetrasubstituted alkenes (**4s**).

We next examined the scope of the reaction with respect to the organometallic reagent (Table 2). We were pleased to find that a broad range of functionalized aryl Grignards provided aryl-BCP products **4t–4ac** in high yields. Alkenyl Grignards were also found to be competent reagents for ring-opening of **1**, providing 1,3-

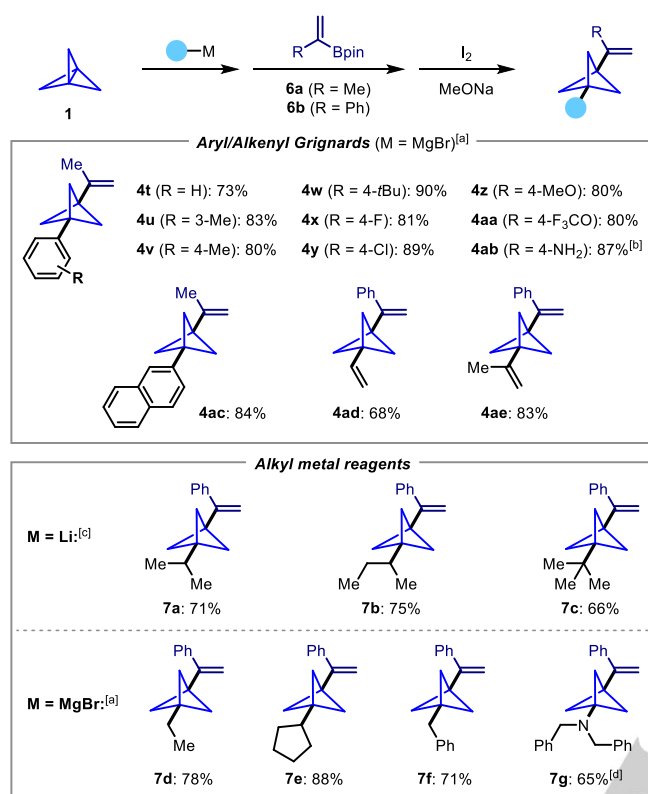
bisalkenyl BCPs **4ad** and **4ae**. To the best of our knowledge, these two examples represent the first reports of ring-opening of **1** with alkenyl Grignard reagents.

**Table 1.** Scope of alkenylboronic esters.<sup>[a]</sup>



[a] Yields are of isolated products. See Scheme 2 for reaction conditions. Products **4f–4m** and **4q–4r** were formed with >95:5 stereoselectivity. [b] Using (*Z*)-hex-1-en-1-ylboronic acid pinacol ester.

Inspired by previous reports of alkylmetal additions to **1**,<sup>[10b,16]</sup> we sought to extend this methodology beyond aryl/alkenyl-substituted BCP synthesis. Therefore, we investigated the addition of a range of alkylolithium reagents to **1** and subsequent Zweifel olefination of the resulting BCP-lithium intermediate (Table 2). Secondary and tertiary alkylolithiums reacted efficiently with **1** at  $-78^{\circ}\text{C}$ , with subsequent high yielding Zweifel olefination giving alkyl BCP derivatives **7a–7c**. On the other hand, primary alkylolithiums (e.g., *n*BuLi) were unreactive at  $-78^{\circ}\text{C}$  and elevated temperatures led only to polymerization of **1**.<sup>[17]</sup> Fortunately, the use of primary alkyl Grignards circumvented this issue and enabled formation of ethyl-BCP derivative **7d** in high yield. Grignard reagents could also be used for the introduction of secondary alkyl (**7e**) and benzyl groups (**7f**). Finally, reaction of **1** with the “turbo amide” pioneered by Baran and co-workers provided amino-BCP **7g** in good yield.<sup>[6a]</sup>

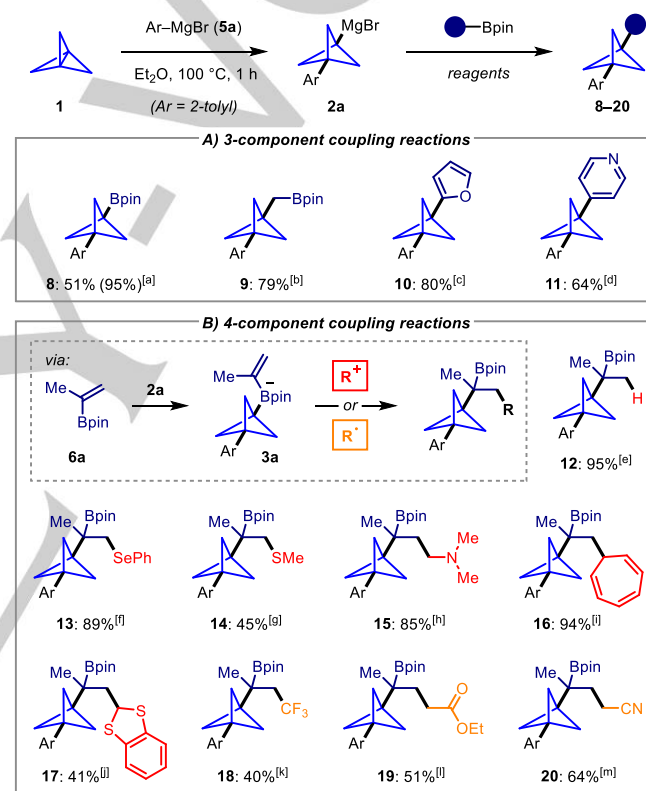
**Table 2.** Scope of alkylmetal reagents.

[a] Using **1** (1.2 mmol) and Grignard reagent (0.60 mmol) in Et<sub>2</sub>O at 100 °C for 1–2 h, then LiCl (0.60 mmol), **6b** (0.30 mmol), I<sub>2</sub> (0.30 mmol) and MeONa (0.90 mmol). [b] Using (4-(bis(trimethylsilyl)amino)phenyl)magnesium bromide. [c] Using **1** (0.30 mmol) and alkyllithium (0.45 mmol) in Et<sub>2</sub>O at –78 °C for 30 min, then **6b** (0.45 mmol) and MeONa (0.90 mmol). [d] Reaction of Bn<sub>2</sub>NMgBr·LiCl with **1** was at RT for 16 h.

To extend the range of BCP-derivatives accessible using this 1,2-metallate rearrangement strategy, we investigated the reaction of BCP-Grignard **2a** with a variety of other boronic ester substrates (Scheme 3A). Reaction with pinacolborane provided synthetically useful BCP-boronic ester **8** in moderate yield.<sup>[12,18]</sup> The low yield is likely a result of the instability of **8** during chromatographic purification, which is supported by isolation of the corresponding alcohol in 95% yield after *in situ* oxidation. Alkylation of **2a** with chloromethylboronic acid pinacol ester gave alkylboronic ester **9** via a Matteson homologation, and arylations of **2a** were possible using our previously reported transition metal-free couplings, forming BCP-furan **10** and BCP-pyridine **11** in good yields.<sup>[19]</sup>

To further demonstrate the diversity of BCP-boronate chemistry for the synthesis of functionalized BCP-derivatives, we extended our approach to four-component coupling reactions (Scheme 3B). Alkenyl BCP-boronate complex **3a**, formed from aryl Grignard **5a**, **1**, and alkenyl boronic ester **6a**, was found to undergo efficient electrophile-induced 1,2-metallate rearrangement with a range of heteroatom- and carbon-based electrophiles under both polar and radical pathways. Electrophiles

included tetrafluoroboric acid, providing tertiary boronic ester **12**; and phenylselenenyl chloride and dimethyl(methylthio)sulfonium tetrafluoroborate, which gave selenide **13** and sulfide **14**, respectively.<sup>[20]</sup> Boronate **3a** was successfully alkylated with Eschenmoser's salt, tropylium tetrafluoroborate, and 1,3-benzodithiolium tetrafluoroborate, forming products **15–17**. Finally, alkylation of **3a** with electron-deficient alkyl iodides was possible using our previously reported photochemical conditions,<sup>[21]</sup> allowing incorporation of trifluoromethyl (**18**), ester (**19**) and nitrile (**20**) groups. Importantly, this four-component coupling reaction provides access to highly functionalized BCP-derivatives containing vicinal quaternary centers; structures that previously could only be accessed via multi-step synthesis.

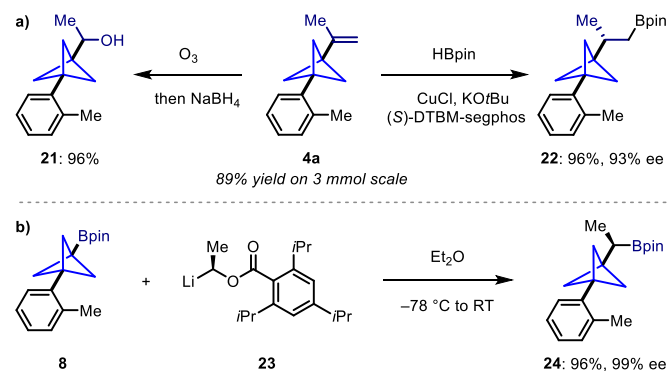


**Scheme 3.** Multi-component reactions of BCP-boronate complexes. *Reagents:* [a] HBpin, aq. HCl, yield in parenthesis is of the corresponding alcohol after *in situ* oxidation with NaOH/H<sub>2</sub>O<sub>2</sub>; [b] ClCH<sub>2</sub>Bpin; [c] furan-2-yl-Bpin, NBS; [d] pyridin-4-yl-Bpin, ClCO<sub>2</sub>CH<sub>2</sub>CCl<sub>3</sub>, NaOH/H<sub>2</sub>O<sub>2</sub>; [e] **6a**, HBF<sub>4</sub>; [f] **6a**, PhSeCl; [g] **6a**, MeSSMe<sub>2</sub>BF<sub>4</sub>; [h] **6a**, H<sub>2</sub>CNMe<sub>2</sub>; [i] **6a**, tropylium BF<sub>4</sub>; [j] **6a**, 1,3-benzodithiolium BF<sub>4</sub>; [k] **6a**, CF<sub>3</sub>I·2DMSO, blue LEDs; [l] **6a**, ICH<sub>2</sub>CO<sub>2</sub>Et, blue LEDs; [m] **6a**, ICH<sub>2</sub>CN, blue LEDs.

The synthetic utility of the three-component coupling process was demonstrated through scaling up the synthesis of **4a** to 3.0 mmol without loss in efficiency (Scheme 4a). Furthermore, high-yielding derivatizations of **4a** provided alcohol **21**, via reductive ozonolysis; and boronic ester **22**, through an enantioselective hydroboration.<sup>[22]</sup> Finally, BCP-boronic ester **8** was homologated via a lithiation–borylation reaction with enantioenriched carbenoid



**23** to give boronic ester **24** in 99% ee (Scheme 4b).<sup>[23]</sup> The catalyst- and reagent-controlled stereoselective syntheses of chiral BCPs **22** and **24** provide attractive alternatives to current approaches to BCPs with  $\alpha$ -stereocenters, which require the use of chiral auxiliaries.<sup>[24]</sup>



**Scheme 4.** Synthetic utility of the BCP-derivatives.

In summary, we have developed a synthesis of 1,3-disubstituted BCP derivatives through a three-component coupling reaction of [1.1.1]propellane with organometallic reagents and organoboronic esters. By taking advantage of the versatile C–C bond forming reactions that are possible via 1,2-metallate rearrangements of boronate complexes, this approach could be applied to the synthesis of alkenyl-, alkyl-, and aryl-BCP derivatives. Furthermore, the strategy was extended to a four-component coupling reaction to access tertiary boronic ester-substituted BCPs containing contiguous quaternary centres. This powerful multi-component reaction strategy, with up to three points of diversification, provides a highly modular approach for the preparation of libraries of structurally diverse BCPs.

## Acknowledgements

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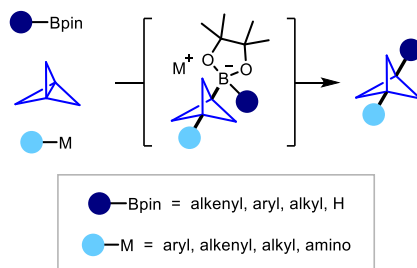
**Keywords:** [1.1.1]Propellane • Bicyclo[1.1.1]pentanes • Multi-Component Reactions • Borylation • Zweifel Olefination

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## COMMUNICATION

A modular synthesis of 1,3-difunctionalized bicyclo[1.1.1]pentanes has been achieved through multi-component couplings between organometallic reagents, [1.1.1]propellane, and organoboronic esters. By utilizing the versatile 1,2-metallate rearrangement chemistry of *in situ* generated boronate complexes, a range C–C bond-forming reactions could be carried out without the need for transition metal catalysis.



- modular synthesis of 1,3-disubstituted BCPs
- transition metal-free 3- and 4-component couplings
- C–C bond formation via 1,2-rearrangements

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